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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/441,723	11/16/99	HILLMAN J	PF-0430-1-DI

EXAMINER	
WELLS, M	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev.11/00)

1- File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/441,723	HILLMAN ET AL.	
	Examiner	Art Unit	
	Matthew O. Wells	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,14-19 and 22-25* is/are pending in the application.

4a) Of the above claim(s) *15-19 and 22-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 14* is/are rejected.

7)☒ Claim(s) 2 is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1, 2, and 14 in Paper No. 6 (received on April 9th, 2001) is acknowledged. The traversal is on the ground(s) that all groups of the invention are closely related and, therefore, would require common areas of search and consideration. This is not found persuasive because the separate classification of the groups is one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is adhered to.

The requirement is still deemed proper and is therefore made FINAL.

2. Newly submitted claims 26-28 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 1-2, and 14 and the new claims 26-28 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the polypeptide of claim 1 can be used in the can be used in a materially different process of affinity purification, diagnostic testing.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution

on the merits. Accordingly, claims 26-28 withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

3. Claims 1 and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection. The claims are drawn to the purified polypeptide sequence comprising the amino acid sequence of SEQ ID NO: 1, wherein the sequence comprises a sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1. This includes alterations of any residue as long as it is not greater than 10% of the residues.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

The instant disclosure of a single species of an amino acid sequence does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera. A description of a genus of polypeptides may be achieved by means of a recitation of a

representative number of polypeptides, defined by polypeptide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). At section B(1), the court specifically states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. The specification proposes to discover other members of the genus by using (beginning in the last paragraph, page 13) conservative changes to the amino acid sequence, wherein a substituted amino acid has similar structural or chemical properties, e.g., replacement of leucine with isoleucine, and more rarely, nonconservative changes, deletions, insertions or both. There is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the amino acids encompassed and no

identifying characteristic or property of the instant amino acids is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific polypeptide sequences and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed and no identifying characteristic or property of the instant polypeptides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Therefore only an isolated amino acid sequence comprising SEQ ID NO: 1, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

4. Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is drawn to a pharmaceutical composition comprising the amino acid sequence of SEQ ID NO: 1. The specification teaches (page 32-34) the use of therapeutically effective dose of compositions that may consist of GSTS, antibodies to GSTS, mimetics, agonists, antagonists, or inhibitors of GSTS, and a pharmaceutically acceptable composition to treat disorders, including cancer (page 27). Although drawn only to cancer, the following is clearly applicable to all of the in vivo diseases recited.

One cannot extrapolate the teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable. Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method comprising the administration of the pharmaceutical composition comprising GSTS, would be used to treat cancer in vivo. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense

mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the pharmaceutical composition would function as claimed. In addition, Hartwell et al (Science, 1997, 278:64-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065). In addition, anti-tumor agents and those that prevent, reduce, retard or eliminate secretion of metastatic promoters, must accomplish several tasks to be effective. They must be delivered into the circulation that supplies the tumor or metastatic promoter producing cells and interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. It is clear, as disclosed above that the specification does not teach how to make/use a formulation with a targeting molecule. Also, the target cell must not have an alternate means of survival despite action at the proper site for the drug. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. The formulation may be inactivated *in vivo* before producing a sufficient effect, for example, by degradation, immunological activation

or due to an inherently short half-life of the formulation. In addition, the formulation may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells and tissues where the formulation has no effect, circulation into the target area may be insufficient to carry the formulation and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to the issues raised above and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

5. If Applicant were able to overcome the rejections recited under 112, first paragraph above, claims 1 and 14 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for SEQ ID NO: 1, does not reasonably provide enablement for a sequence at least 90% identical to SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The claims are drawn to a purified GSTS polypeptide, wherein the sequence comprises a sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 1. This includes amino acids with alterations in X number of nucleotides which includes truncations, deletions, mutations and substitutions of nucleotides, not to exceed 10% of the amino acid sequence of SEQ ID NO: 1. The specification teaches (beginning on page 14, last paragraph) that the GSTS amino acid sequence can differ

from the amino acid sequence of SEQ ID NO: 1; being at least 80% identical. These variant sequences are compared using computer programs to determine the degree of identity between the variant sequence and the amino acid sequence of SEQ ID NO: 1. On page 13, last paragraph, sequence identity is defined as the degree to which the polypeptide sequences are able to maintain biological or immunological activity. One cannot extrapolate the teaching of the specification to the scope of the claims because the specification provides neither guidance on nor exemplification of how to make a polypeptide which is at least 90% identical to the amino acid sequence of SEQ ID NO: 1, a polypeptide that could have at least X number of amino acid alterations, that will function as contemplated. The specification also does not teach how to use a polypeptide which is altered by up to 10%, with X number of amino acid alterations, that does not function as contemplated. It is well known in the art that protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Burgess et al. J of Cell Bio. 111:2129-2138, 1990. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Lazar et al. Molecular and Cellular Biology 8:1247-1252 (1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Further, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed polypeptide can be tolerated that will allow the polypeptide to function as

contemplated. Further, Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and given the lack of information in the disclosure, it cannot be predicted, with a reasonable expectation of success, which of the X amino acids can be altered and still produce a product that will function as contemplated or how to use the sequence if it does not function as contemplated. Therefore, in view of the speculative nature of the invention, the lack of predictability of the prior art, the breadth of the claims and the absence of working examples, it would require undue experimentation for one skilled in the art to make or use the invention as claimed.

6. Claims 1 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1 recites an activity without defining what activity is to be measured. It is unclear if a biologically active fragment is a fragment that is antigenically, immunogenically, chemotactically, enzymatically, etc., active fragment.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Harris et al., "A novel glutathione transferase (13-13) isolated from the matrix of rat liver mitochondria having structural similarity to class Theta enzymes", Biochem. J. (1991) 278, 137-141.

Claim 1 is drawn to a purified polypeptide comprising an amino acid sequence, wherein the amino acid is a biologically-active or immunogenic fragment of the amino acid sequence of SEQ ID NO: 1.

Harris et al. disclose an amino acid sequence for the novel glutathione transferase (GST 13-13) in figure 5, page 140. The sequence disclosed by Harris comprises a sequence (amino acids 8-18) (ELFYDVLSPYS), which have 100% sequence similarity to the portion of the claimed sequence of SEQ ID NO: 1, amino acids 9-19.

Harris et al., disclose (page 138, first column) that the immunoreactivity of the GST was determined by Western blotting using polyclonal antibodies. Harris et al., disclose (page 140, first column) that the GST 13-13 "had a specific activity of 82 units/mg with CDNB (1-chloro-2,4-dinitrobenzene) and 26 units/mg with ethacrynic acid."

Harris et al. disclose (pages 137-138) the composition comprising the GST protein in a pharmaceutically acceptable buffer, sodium phosphate.

In view that Harris et al. disclose a polypeptide which comprises 11 consecutive amino acids of applicant's SEQ ID NO: 1, the disclosure of Harris et al. is deemed to anticipate the claimed immunogenic and biologically active fragments.

9. Claim 1 is rejected under 35 U.S.C. 102(a) as being anticipated by Hillier, L. et al., Genbank Sequence Database (Accession AA291397), National Center for Biotechnology Information, National Library Medicine, Bethesda, MD 20894, 08 Aug 1997.

Claim 1 is drawn to a purified polypeptide comprising an amino acid sequence, wherein the amino acid is a biologically-active or immunogenic fragment of the amino acid sequence of SEQ ID NO: 1.

The sequence disclosed by Hillier et al. comprises a sequence (amino acids 1-67), which have 100% sequence similarity to the portion of the claimed sequence of SEQ ID NO: 1, amino acids 140-207.

In view that Hillier et al. disclose a polypeptide sequence which comprises 67 consecutive amino acids of applicant's SEQ ID NO: 1, the disclosure of Hillier et al. is deemed to anticipate the claimed immunogenic and biologically active fragments.

Allowable Subject Matter

10. Claim 2 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Matthew O. Wells whose telephone number is 703-308-4521. The examiner can normally be reached on M-F (7:00-4:30), every other Monday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Matthew Wells
May 31, 2001

MARK NAVARRO
PRIMARY EXAMINER